139. The method of claim 82, wherein five nanomolar of said polypeptide elicits less than one-fold stimulation over background in NIH/3T3 cells.

140. The method of claim 114, wherein said polypeptide stimulates a greater difference in fold stimulation of BALB/MK keratinocyte cells relative to NIH/3T3 fibroblasts when compared to the difference in fold stimulation of BALB/MK cells relative to NIH/3T3 cells stimulated by epidermal growth factor (EGF), transforming growth factor-alpha (TGF-alpha), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF), as measured by percent of maximal H^3-thymidine incorporation.

141. The method of claim 114, wherein five nanomolar of said polypeptide elicits less than one-fold stimulation over background in NIH/3T3 cells.--

REMARKS

Applicants thank Examiner Saoud for her explanation of the current status of the claims. However, applicants would appreciate confirmation that the amendment filed December 3, 1998 has been entered. Applicants understand that claims 38-131 are pending and under examination. Applicants also understand that recitations of methods of inhibiting by administration of heparin or a peptide are withdrawn from consideration. Applicants herewith cancel claims 122, 127 and 130, without prejudice or disclaimer and add new claims 132-141. Thus, with the entry of this

amendment, claims 38-121, 123-126, 128, 129 and 131-141 are active in this case.

I. SUBSTITUTE SPECIFICATION

Applicants herewith submit a Substitute Specification and a marked-up copy of the original specification showing where all changes have been made. All of the Examiner's concerns have been addressed in the Substitute Specification. Applicants attest that no new matter has been added with the Substitute Specification.

II. CLAIM OBJECTIONS

The Examiner's objections to claims 126, 127 and 129 have been addressed in the above amendment. Consequently, these objections should be withdrawn.

III. REJECTIONS UNDER 35 USC § 112

The Examiner rejects claims 38-56, 57-72, 82-101 and 114-120 under 35 USC § 112, first paragraph, for the alleged reason that: "...because the specification, while being enabling for KGF and KGF polypeptides which have an amino acid sequence as set forth in Figure 7, or is truncated within the region of amino acids 32-78, does not reasonably provide enablement for any protein that (1) has a recited molecular weight, produced by fibroblast cells and has a specific activity as recited in the claims or (2) comprises a segment of the amino acid sequence of Figure 7." (Office Action of July 19, 1999, Paper No. 20, page 5, paragraph 7) The Examiner contends that the specification does not enable any person skilled in the art

to which it pertains to use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection as it may apply to the claims, as amended above.

First, applicants have amended claims 38, 49 and 114 to recite "amino acids 32-78 of Figure 7" thereby addressing the Examiner's concern about essential features of the invention. Applicants have amended claims 64, 69, 88, 90 and 95 to clarify that amino acids 32-78 confer epithelial cell specificity on the KGF polypeptide. Applicants also have amended claims 57 and 82 to further define what is included by the term "segment" and to address the Examiner's concern about the essential features of the invention.

In paragraph 8, the Examiner states that the specification fails to enable claims 49-56 and 82-109 (directed to methods of accelerating or improving the healing of a wound in a patient), claim 110 (directed to a method of inhibiting keratinocyte growth factor activity *in vivo)* and claims 121-131 (directed to a method of treating a patient having an epithelial skin condition). The Examiner admits that the specification enables the use of KGF and related pharmaceutical compositions for stimulating epithelial cells either *in vivo* or *in vitro*. However, she argues that the "...knowledge gained from the specification that KGF stimulates epithelial cells is not sufficient for a claim to accelerating or improving the healing of a wound" because such a method is not provided for in the instant specification and because there is no evidence to support the conclusion that all epithelial skin conditions are caused by an over-expression of KGF. (Office Action at page 10) Applicants respectfully traverse this rejection.

The present application describes an invention that is pioneering in nature, *i.e.*, it describes and claims a novel molecule, KGF, that has unique properties related to its specificity for epithelial cells. Although the protein and DNA encoding such protein were novel, methods of preparing pharmaceuticals for use in treating wounds and conditions associated with excessive cell growth, in general, were known in the art at the time of the invention. Applicants have previously pointed out that although KGF is unique in structure and function, it is a member of a family of growth factors which includes acidic fibrolast growth factor (aFGF), basic fibroblast growth factor (bFGF) and the related products of the *hst* and *int*-2 oncogenes. At the time of the invention, the literature reported several examples of growth factors within the FGF family that displayed *in vivo* pharmaceutical wound healing activity. For example, Stenberg *et al., J. Surg. Res.* 50: 47 (1991) reported an enhancement of wound healing by topical treatment of basic fibroblast growth factor (bFGF) applied to an area contaminated with bacterial over-growth. Hebda *et al., J. Invest. Dermtol.* 95: 626 (1990) describes the acceleration of epidermal wound healing effects when recombinant human bFGF is injected into or topically applied to pigs. A further *in vivo* study of Tsuboi *et al. J.Exp. Med* 172: 245 (1990) describes the stimulatory wound healing effects when recombinant bFGF is applied locally to healing-impaired mice. All of this art, which is already of record in this case (submitted December 10, 1996), is contemporaneous with the present invention and supports the enablement of applicants' claimed invention.

The *in vivo* use of KGF in numerous animal models has been demonstrated. Staiano-Coico, *et al. J. of Exp. Med.* 178:865-878 (1993)

showed the effects of KFG in epidermal wound healing using a porcine model. More recently, Danilenko *et al., Am. J. of Pathology* 147(5): 1261-1277 (1995) (Copy attached) has demonstrated that the application of KGF resulted in significant acceleration of healing in several animal models of wound repair. Applicants have previously submitted evidence of the use of KGF in vivo in a variety of contexts. For instance, Pierce *et al., J. of Exp. Med.,* 179: 831-840 (1994) (copy previously submitted) showed the effects of KGF in stimulating skin cells to proliferate and differentiate in rabbit models, Thomason, A., "Peptide Growth Factors in the GI Tract ," *Abstract of American Gastroenterology Association Meeting* (June 1994) (copy previously submitted) reported the effects of KGF in stimulating the proliferation of epithelial cells in the intestinal system. Panos, R. "Keratinocyte Growth Factor (KGF) prevents hyperoxia-induced mortality in rats," *Abstract, ATS, International Conference* (May, 1995) reported the effects of KGF in repairing lung tissue in rats (copy previously submitted). Other examples have been provided in the response filed December 10, 1996.

Applicants further argue that the law does not require one to exemplify every embodiment of the invention. Likewise, it is permissible, if not preferable to rely upon what was known in the art at the time of the invention. In view of the ample evidence provided above and the legal requirements for enablement, applicants respectfully request the Examiner to reconsider and withdraw this rejection.

The Examiner also argues that claims 121 and 126 are generic and therefore improper. In response, applicants have amended these claims to

incorporate recitations in dependent claims. Applicants accordingly request the examiner to withdraw this rejection.

The Examiner rejects claims 110 and 121-128 due to an alleged skepticism with regard to the use of antibodies. Applicants respectfully assert that the Examiner's rejection speaks more of "utility" than enablement. In further response, applicants direct the Examiner's attention to the work of Alarid *et al, Proc. Natl. Acad. Sci. USA* 91: 1074-1078 (1994) (copy attached), which describes the use of KGF-neutralizing monoclonal antibody to inhibit seminal vesical growth and morphogenesis in organ cultures and to the work of Sugimura, *Int. J. Devl. Biol.* 40: 941-951 (1996), which show the use of neutralizing antibodies against KGF in the inhibition of cell growth and morphogenesis in the rat prostate (copy attached). Finally, applicants provide copies of Weiner, "An Overview of Monoclonal Antibody Therapy of Cancer" *Seminars in Oncology*, 26: 41-50 (1999) and Weiner, "Monoclonal Antibody Therapy of Cancer" *Seminars in Oncology* 26: 43-51 (1999), which support the use of antibodies in clinical settings. The above literature should resolve any doubt about the potential efficacy of antibodies for use within the scope of the claimed invention.

The Examiner further alleges that the specification fails to show an adequate bioassay for use in permitting the skilled artisan to extrapolate to *in vivo* therapeutics. Applicants respectfully disagree and direct the examiner's attention to the BALB/MK assay described throughout the specification. However, applicants further point out that other assays could also be employed to carry-out the method of the invention and that such assays are well known in the art. In that regard, applicants direct the

examiner's attention to the assays in the work described above, *see e.g.* Hebda and Stenberg.

The Examiner also states that the specification fails to enable the use of a DNA probe in the claimed methods. Applicants respectfully traverse this rejection and direct the Examiner's attention to the use of DNA probes in the specification, e.g. at page 58. Probes of this type detect the antisense of an encoding sequence. It is well known in the art that the antisense of DNA encoding sequence prevents transcription. Thus, the novel methods that encompass the use of DNA probes apply technology that is well known in the art.

In paragraph 9, the Examiner objects to the functional language used throughout the claims. Applicants point out that the functional language is fully supported in original Table I-2 in the application, as filed. Support for new claims 133, 135,137, 139 and 141 can be found in the original specification at page 47, lines 5-10. Applicants further explain that with the different functional tests (see, e.g. claims 39, 40, 41, 133) they do not intend to provide for KGF peptides that have differing ability to stimulate BALB/MK cells, (i.e., have different functional properties). Rather, applicants have added the differing functional recitations to provide alternative tests for what does or does not fall within the scope of the claims. If a single polypeptide meets the functional limitation of one of the dependent claims, it also meets the functional limitation of the parent claims. The various functional recitations are simply alternative definitions of the term "has preferential mitogenic activity on cells of epithelial origin."

In paragraph 12, the Examiner raises a number of rejections under 35 USC § 112, second paragraph. Applicants assert that all of the Examiner's

objections have been addressed with the above amendment. For instance, applicants have deleted "in vivo" in claims 38,57 and 110. Applicants have added that the molecular weight was determined by SDS PAGE under reducing conditions in claims 38, 48, 49, 56, 114 and 120. Claims 57 and 82 have been amended to clarify what is meant by "segment". In view of these amendments, applicants respectfully request the examiner to withdraw the § 112, second paragraph rejections.

IV. ALLOWABLE SUBJECT MATTER

Applicants acknowledge the Examiner's indication that claims 73-81 would be allowed if re-written in independent form and that claims 111-113 are allowed.

CONCLUSION

Applicants respectfully assert that in view of the above amendment and explanations, all the remaining pending claims are in condition for allowance. Indication of allowability of all the claims is therefore respectfully awaited.

Respectfully submitted,

December 28, 1999
Date

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